

## REMARKS

Claims 3, 5, 6 and 12 and claims 3, 4, 7-11, 13 and 14 as amended, are presented in this response for the Examiner's review and consideration. Although the Applicants maintain their traverse of the restriction requirement, Claims 4, 7-11 and 14 have been amended to comply with the Examiner's request that they depend from elected claim 3.

### Objection to the Specification

The Examiner has objected to typographical errors in the specification related to the numbering of the figures. The first figure presented was incorrectly labeled as figure 2. That figure as well as references to it have been properly re-labeled as Figure 1. All other figures and references to them have been correspondingly adjusted so that the figures are now labeled sequentially from 1 to 6. Applicants believe that the specification amendments presented above in this response to address the Examiner's objections and add no new subject matter.

### Rejection Under 35 USC § 112, First Paragraph

The Examiner has rejected claim 3 as failing to comply with the written description requirement of 35 U.S.C. § 112, first paragraph. The Examiner has particularly cited page 7, lines 4-13 in the specification in which Applicants define a strongly chaotropic agent in relation to 1.5 M sodium perchlorate and 6 M or greater urea or guanidine HCL and indicates that the specification is deficient for not naming other strongly chaotropic agents.

The Applicants' claim 3 requires cross-linked allophycocyanin that has not been exposed to strongly chaotropic agents after cross-linking. The Applicants submit that the definition of strongly chaotropic as supplied in the Applicants' specification provides sufficient guidance to one skilled in the art to select conditions in which the cross-linked allophycocyanin is not exposed to a strongly chaotropic agent. Chaotropism, as defined by the on-line Stedman's

Medical Dictionary, relates to the property of ions to disrupt the structure of water and thereby promote the unfolding of proteins. This is a physically observable phenomenon. Further the Applicants' definition not only supplies the identities of two types of ions which are considered strongly chaotropic but also the ion strength of a strongly chaotropic solution of these ions in molarity which is a basic measure of ion strength introduced in general chemistry courses. Thus the Applicants provide specific guidance as to conditions which should not be used. Applicants are not aware of any requirement which mandates encyclopedic listing of all conditions to avoid.

The Examiner has rejected Claims 3-14 under 35 U.S.C. § 112, first paragraph for lack of enablement because in the Examiner's view the specification does not reasonably provide enablement for other strongly chaotropic agents and for the fact the Applicants have disclosed a comparison of 1.5M sodium perchlorate to 6 M or greater urea or guanidine HCL. As stated above the Applicants provided the definition of strongly chaotropic agents to clarify conditions that are to be avoided. Thus, the Applicants have provided the exemplary examples cited by the Examiner to describe the conditions to be avoided.

As the Examiner has stated on page 5, lines 8 and 9, "[E]nablement requires that the specification teach those in the art to make and use the invention without undue experimentation." The Applicants have provided an exemplary embodiment using sodium perchlorate at about 1 M which the Examiner has acknowledged. This embodiment fulfills the requirements of the claims. However, the Examiner states: "Typical denaturants which may be used in this format are sodium perchlorate preferably at a concentration about 1 M. However, it does not disclose the use of other strongly chaotropic agents other than sodium perchlorate (Office Action page 6, lines 7-9, emphasis added.) Thus, it would appear that the Examiner has

misinterpreted 1 M sodium perchlorate as a strongly chaotropic agent; such an interpretation is contradictory to the plain language of lines 1-13 of page 7 of the specification which define a strongly chaotropic agent, indicate that strongly chaotropic agents are not to be used; indicate that a more gentle denaturant is to be used; and provide the identity of a suitable denaturant and an ion strength of that entity in the well known chemical unit of molarity, e.g. 1 M sodium perchlorate. Further, the gentle denaturant is characterized as not affecting the 650/620 and 650/280 nm ratios as compared to the native APC (allophycocyanin). (Specification, p. 7, lines 1-3. Also, see example 1, page 11.)

The Applicants submit that for at least the reasons that a specific example of a suitable gentle denaturant is provided, and specific measurable spectroscopic parameters are identified for the APC after treatment, that Applicants have provided enablement and respectfully request that the Examiner withdraw his rejections under 35 U.S.C. § 112 first paragraph for lack of written description and enablement.

The Examiner has rejected claims 3-14 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter of the invention. Specifically, the Examiner has objected to the phrase “used according to this invention” in claim 3 and recommends that it be removed from the claim. The Applicants have amended claim 3 accordingly.

The Applicants believe that the phrase “having the ability” in claim 3 implies the positive property of the ability to absorb light energy. Further the claim specifically includes the limitations that the energy transfer be in a time resolved manner. Accordingly, Applicants request that the Examiner withdraw his rejection of claim 3 based on the phrase “having the ability”.

The Examiner has further objected to the term “strongly” in claim 3. As discussed in detail above Applicants have provided a definition with specific examples of the meaning of “strongly” as used with the chaotropic agent in the context of this application.

The Examiner indicates a lack of antecedent basis for term “the donor molecule” in claim 4. Claim 4 has been amended to “donor compounds” which is referenced in claim 3.

The Examiner has objected to the ratio of areas and “at least 4” in claim 9 as vague and indefinite. The ratio is stated in claim 9 to be the area under the absorbance spectrum between 500-700 nm to the area between 250-300 nm of at least 4. Applicants submit that comparisons of the area under the peaks in one region of an absorbance spectrum to the area under the peaks in a second region of the spectrum is well-known in the art and has the practical value of providing a reproducible comparison without the need for detailed specification of instrumentation parameters for making the measurement. Those skilled in the art recognize that when a single number is referenced stating a ratio that the second number of the ratio is implied to be 1, e.g., a ratio of 4 is equivalent to a ratio of 4:1. For at least the reasons discussed above the Applicants request that the Examiner withdraw his objections to claims 3-14 under 35 U.S.C. § 112, second paragraph.

Rejection Under 35 U.S.C § 103 (a)

The Examiner has rejected claims 3-6, 9 and 10 under 35 U.S.C. § 103 (a) as being unpatentable over Park in view of Ong. The Examiner has stated that Park discloses measuring the energy transferred from donor compounds to absorb light energy and then transfer this energy to cross-linked allophycocyanin and the use of europium but does not disclose the need to expose cross-linked allophycocyanin to strongly chaotropic agents after cross-linking. (Office

Action page 8, last 2 paragraphs). The Examiner then cites Ong for use of the strong chaotropic agent 8 M urea. (Office Action page 9, first paragraph).

The Examiner has mischaracterized the Applicants' invention, as Applicants' claims require allophycocyanin which has not been exposed to strongly chaotropic agents. Thus, the Examiner has identified a deficiency and identified a reference (Ong) which in fact teach away from the Applicants' invention. Therefore combination of Ong with Park is not proper because the deficiency in Park asserted by the Examiner and "support" of Ong is in direct opposition to the requirement of the Applicants' claims.

Further as discussed in the specifications on page 2, lines 24-29 and page 3, lines 1 and 2 and shown in Figures 1B and 1C, cross-linked and stabilized allophycocyanin prepared by the methods of Ong have a reduced ratio of fluorescence at 650/620 nm as compared to native APC. Whereas allophycocyanin treated by the Applicants' method has 650/620 and 650/280 absorbance ratios comparable to the native APC. (Specifications, page 7, lines 1-3). Thus, the Applicants' method which avoids treatment with strong chaotropic agents produces an allophycocyanin preparation that manifests an absorbance behavior significantly different than allophycocyanin preparations prepared by the methods of Ong. Accordingly, the Applicants request the Examiner withdraw his rejection of claims 3-6, 9 and 10 under 35 U.S.C. § 103 (a).

The Examiner has rejected claims 11-14 under 35 U.S.C. § 103 (a) as being unpatentable over Park and Ong in view of Applicants' admission of prior art. The Applicants respectfully submit that claims 11-14 which now depend from claim 3 (as amended) are for an improved method. The Applicants have disclosed on Page 1, lines 25-30 and Page 2, lines 1-3 of the specification that native APC disassociates under typical assay conditions which results in a shift in fluorescence from 660 nm and a drop in fluorescence intensity. Park does not address this

problem. Ong's method as described on Page 2 of the specification provides for stabilized, cross-linked allophycocyanin but suffers at least the deficiency of having a reduced ratio of fluorescence of 650/620 nm verses the native APC. The Applicants' improved method of claim 3 and related dependent claims provides the advantage of enhanced stability and fluorescence ratios of 650/620 and 650/280 that are comparable to the native APC. (Specification page 7, lines 1-3.) Thus, the Applicants have identified deficiencies in the methods of Park and Ong and provided the claimed method which addresses the identified deficiencies and provides an improved method. Accordingly, Applicants respectfully request that the Examiner withdraw his rejection of claims 11-14 which depend from claim 3 under 35 U.S.C. 103 (a).

### CONCLUSION

For at least the reasons set forth above, Applicants respectfully submit that claims 3-14 are in condition for allowance. Applicants therefore request that the claims be allowed.

It is believed that no fee other than the fee for the one month extension of time is due with this response. However, if any additional fees are determined to be due, the Director is hereby authorized to charge these fees to the undersigned's Deposit Account No. 50-0206.

Respectfully submitted,

Hunton & Williams

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